UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/774,681 | 02/01/2001 | Linda A. Sherman | 313332000101 | 3045 |

21874 7590 05/13/2008

EDWARDS ANGELL PALMER & DODGE LLP
P.O. BOX 55874
BOSTON, MA 02205

| EXAMINER | |
|---|---|
| SCHWADRON, RONALD B | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 05/13/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/774,681 | SHERMAN ET AL. | |
| | Examiner | Art Unit | |
| | Ron Schwadron, Ph.D. | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *6-35* is/are pending in the application.

4a) Of the above claim(s) *6,18-21,31 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-17,22-30,32,33,35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/1/08 has been entered.

2. Regarding applicant's comments about claim 30, applicant indicated in the response of 12/6/06 that said claim was drawn to nonelected subject matter. Said claim will now be examined.

3. Claims 7-17,22-30,32,33,35 are under consideration.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 7-17,22-30,32,33,35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants arguments have been considered and deemed not persuasive.

a)There is no support in the specification as originally filed for the recitation in claim 32 of "further comprising a polypeptide spacer between the TCR variable domain and the transmembrane and cytoplasmic region of a CD3, CD8, or CD16 receptor". Regarding applicants comments about the specification, page 6, lines 10-14, said passage discloses a particular construct in Figure 1 that uses a CD8 hinge. Said passage does not disclose use of a "polypeptide spacer" other than CD8 hinge and is restricted to a disclosure of the particular construct referred to in said Figure. Claim 32 is not restricted to a nucleic acid encoding the construct disclosed in Figure 1 and

encompasses use of a polypeptide spacer other than CD8 hinge and is therefore broader in scope than the actual disclosure of the specification.

Regarding applicants comments about the specification, page 6, lines 10-14, said passage discloses a particular construct in Figure 1 that uses a CD8 hinge. Said passage does not disclose use of a "polypeptide spacer" other than CD8 hinge and is restricted to a disclosure of the particular construct referred to in said Figure. Claim 32 is not restricted to a nucleic acid encoding the construct disclosed in Figure 1 and encompasses use of a polypeptide spacer other than CD8 hinge and is therefore broader in scope than the actual disclosure of the specification. Regarding page 6, line 11 of the specification, said sentence refers to the CD8 region spacer of the previous sentence.

b) There is no support in the specification as originally filed for the molecules of claim 26/27. Said molecules encompass nucleic acids encoding molecules that contain a polypeptide spacer and CD8 hinge wherein there is no disclosure of such molecules in the specification as originally filed.

c)There is no support in the specification as originally filed for the recitation of "CD8 hinge" in claim 35. The specification, page 6, lines 10-14, discloses a particular construct in Figure 1 that uses a CD8 hinge. Said passage does not disclose use of a "CD8 hinge" other than the particular CD8 hinge sequence disclosed in Figure 1. There is no disclosure in the specification as originally filed of the use of "CD8 hinge" spacers other than the specific sequence disclosed in figure 1, yet the claim encompasses use of "CD8 hinge" sequences other than that specifically disclosed in specification.

There is no written description of the scope of the claimed inventions in the specification as originally filed (aka the claimed inventions constitute new matter).

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 11-14,24-27 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11,24-27 are indefinite in that they lack antecedent basis in claim 32. The molecule of clam 32 has **a spacer** between the TCR variable domain and the zeta region whilst said spacer is absent in the molecule of claim 11/24-27. For the purposes of prior art, the claims will be interpreted as containing all of the components of claim 32.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 7-17,23-25,28-30,32,33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al. in view of Sette et al.

Chung et al. teaches a nucleic acid encoding a single chain TCR alpha and beta chain joined by the linker of claim 12/32 (see Figure 1) wherein the construct also includes the ζregion of CD3 and wherein the variable region and ζchain are joined by a polypeptide spacer (. see Figure 1 wherein CB would constitute a linker and see Materials and Methods section, pages 12654-12655). Chung et al. teach expression vectors encoding nucleic acids comprising a leader sequence and said TCR, and T cells containing said vectors and methods of making the aforementioned (see Materials and Methods wherein BW is a T cell line and Figure 1). Human CD3 ζ region is well known in the art. The aforementioned sequence has a leader sequence (see Figure 1). Chung

et al. does not teach use of a nonhuman TCR which is HLA A2 restricted. Chung et al. discloses that the TCR can be derived from known T cells and that said chimeric TCR can be used for diagnostic and therapeutic purposes (see page 12658, first column). Sette et al. disclose the use of HLA A2 transgenic mice that produce T cells with nonhuman TCR that are HLA A2 restricted (see page 5588, second column). Said system has the advantage that T cells can be produced by immunizing mice using methods not acceptable in humans (for example immunization of antigen with IFA used in the example, page 5587, second column). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Chung et al. teaches the claimed invention except for use of nonhuman TCR, whilst methods of generating nonhuman TCR that were HLA A2 restricted were known in the art. One of ordinary skill in the art would have been motivated to do the aforementioned because Chung et al. discloses that their TCR can be derived from known CTL and used in diagnostic or therapeutic methods and the method of Sette et al. can be used to produce T cells using effective immunization methods not acceptable in humans.

Regarding applicants comments about claim 32, all of the limitations of claim 32 were addressed in the instant rejection as per enunciated in the previous Final Office action. Regarding applicants comments about use of CD8 or CD16 receptor, the claims all encompass use of CD3 as per claim 7. The Examiner is not required to address all members of a Markush group recited in a single claim. All of the limitations of claim 32 and dependent claims have been addressed as required. Regarding applicants comments, Sette et al. teach TCR with the specificity recited in the claims wherein said TCR could be cloned using art known technologies. Chung et al. teach the general applicability of their scTCR to TCR molecules per se (see page 12658). Regarding applicants unsupported allegations about the operability of the prior art references, the MPEP section 2145, section I. discloses:

*The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from*

*common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.").*

Regarding applicants comments about Sette et al., the T cell response disclosed in Table 1 is "human HLA restricted" (aka HLA A2.1 restricted ) as per recited in the claims under consideration (aka the peptides *bind HLA A2.1* and are recognized by *TCR* which bind said complex). The Kb portion of the chimeric MHC molecule does not bind TCR, it binds mouse CD8 (see page 5589, first column). Thus, the TCR generated bind peptide in the context of HLA 2.1. Regarding applicants comments, Sette et al. disclose that the human HLA restricted transgenic mouse model yields results that generally correlate with immunogenicity (see abstract). Sette et al. disclose mice with TCR that recognize tumor antigens in the context of HLA A2.1 (for example HPV in Table 1). The growth of T cell lines from immunized animals is routine technology (see Danska et al. from IDS filed 3/8/05). Furthermore, the method disclosed by Sette et al. is essentially the same as that used by applicant in the specification. In addition, the constructs would have a wide variety of potential art recognized uses for research purposes.

10. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al. in view of Sette et al. as applied to claims 7-17,23-25,28-30,32,33 above, and further in view of Disis et al.

The previous rejection renders obvious the claimed invention except wherein the tumor associated antigen is Her2/neu. Chung et al. teaches that the recombinant TCR can be used for therapeutic or diagnostic purposes. Disis et al. teach that HER-2/neu is a cancer cell antigen recognized by T cells. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because the previous rejection renders obvious the claimed invention except wherein the tumor associated antigen is Her2/neu, whilst Chung et al. teaches that the recombinant TCR can be used for therapeutic or diagnostic purposes and Disis et al. teach that HER-2/neu is a cancer cell antigen recognized by T cells.

Applicants arguments are as per addressed above. In addition, Sette et al. disclose that the human HLA restricted transgenic mouse model yields results that generally correlate with immunogenicity (see abstract).

11. Claims 26,27,35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chung et al. in view of Sette et al. as applied to claims 7-17,23-25,28-30,32,33 above, and further in view of Moritz et al. (PNAS USA 1994). The previous rejection renders obvious the claimed invention except wherein the spacer is a CD8 hinge. Moritz et al. disclose a chimeric molecule containing an antigen recognition moiety, a CD8 hinge (encompassing the CD8 hinge recited in the claims) and the ζregion of CD3 (aka ζ chain of the TCR) wherein the CD8 hinge is required in order for the chimeric molecule to mediate cell signaling upon transfection into a cell. A routineer would have substituted said region for the CB portion of the molecule taught by Chung et al. in view of the demonstration that said molecule allows signaling mediated by an antigen recognition moiety/ζregion of CD3 chimeric receptor. It would have been prima facie obvious to one of ordinary skill in the art at the time to have created the claimed invention because the previous rejection renders obvious the claimed invention except wherein the spacer is a CD8 hinge, whilst Moritz et al. disclose a chimeric molecule containing an antigen recognition moiety, a CD8 hinge (encompassing the CD8 hinge recited in the claims) and the ζregion of CD3 (aka ζ chain of the TCR) wherein the CD8 hinge is required in order for the chimeric molecule to mediate cell signaling upon transfection into a cell. In KSR Int'l Co. v. Teleflex Inc., 550 U.S. m, 2007 WL 1237837, at "13 (2007) it was stated that "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill". As per above, a routineer would have substituted said region for the CB portion of the molecule taught by Chung et al. in view of the demonstration that said molecule allows signaling mediated by an antigen recognition moiety/ζregion of CD3 chimeric receptor.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday-Thursday 7:30-6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen O'Hara can be reached on 571 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ron Schwadron, Ph.D./
Primary Examiner
Art Unit 1644